**Remarks**

Claims 21-28, 32, and 51-53 are presently under examination, claims 1-9, 29-31, 33-38, and 48-50 having been previously canceled and claims 10-20 and 39-47 having been previously withdrawn.

Applicants note that the objection to the Abstract has been withdrawn.

Applicants note that the 112, indefiniteness rejection appears to have been withdrawn.

Applicants note that the 35 U.S.C. § 102(b), anticipation rejection of claims 25-27 as to Bjorbaek (WO 00/66721) appears to have been withdrawn.

Applicants note that claim 28 is free of the art.

Applicants thank Examiner Krishnan for the courtesy of the telephonic interview conducted June 19, 2007.

**Response to Rejection of Claims 21-28 and 32 under 35 U.S.C. § 112, first paragraph, enablement**

Claims 21-28 and 32 stand rejected as allegedly lacking enablement. It is the view of the Examiner that the specification is enabled for the treatment of prostate and breast cancer using the compound of formula III and antisense oligonucleotides and interfering oligonucleotides, but does not reasonably provide enablement for the treatment of all other types of cancers using the compound of formula III and the treatment of cancers using any other Rsk specific inhibitor. The Examiner then cites a series of Wands factors as to claims 21 and 25, but does not address other rejected claims (22, 23, 24, 26, 27, 28, and 32) in the Wands discussion.

The Examiner asserts that, regarding the breadth of the claims, claim 21 is drawn to a method of treating cancer characterized by excessive Rsk activity, comprising administering a composition comprising a compound of formula III, and that claim 25 is drawn to the same method comprising administering an Rsk specific inhibitor. The Examiner then asserts that these claims encompass treating **all** types of cancers/tumors with **any** Rsk specific inhibitor (emphasis added).

The Examiner, at the bottom of page 5, asserts that, regarding the existence of working examples, only one compound (SL0101-1) was tested against human and prostate cancer, and that the evidence is not commensurate in scope with the claimed invention and does not

demonstrate criticality of a claimed range of compounds of formula III and numerous and various cancers, and also any Rsk specific inhibitor. The Examiner does not state which claims he is referring to in reference to formula III, numerous and various cancers, or any Rsk specific inhibitor. Applicants note that independent claim 21 recites general formula III, and its dependent claims 22, 23, and 24 recite specific side groups of formula III and dependent claim 32 recites administering additional anti-tumor therapy, while independent claim 25 does not specifically recite formula III, nor does its dependent claims 26, 27, and 28.

Applicants note that only independent claim 21 and independent claim 25 are specifically referred to by the Examiner in the rejection of claims 21-28 and 32. Applicants assert that Examiner should also address each of the dependent claims of independent claim 21 (i.e., 22, 23, 24, and 32) and independent claim 25 (i.e., 26, 27, and 28) specifically to indicate why Examiner has rejected those claims as not enabled.

Applicants traverse the rejection for the following reasons.

It is well-settled that an applicant need not have actually reduced the invention to practice prior to filing in order to satisfy the enablement requirement under 35 U.S.C. §112, first paragraph. MPEP §2164.02 (citing *Gould v. Quigg*, 822 F.2d 1074 (Fed. Cir. 1987)). Indeed, the invention need not contain a single example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation (*In re Borkowski*, 422 F.2d at 908), and "representative samples are not required by the statute and are not an end in themselves" (*In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970)). Thus, 35 U.S.C. § 112, first paragraph, enablement does not require any working examples.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)). The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* Further, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. MPEP §2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Therefore, under current law, enablement does not require a working example and experimentation is allowed so long as it is not undue.

Additionally, under the present law of enablement, claims reciting large numbers of species are allowable without disclosure of every species so long as the art engages in experimentation to identify the operative species encompassed by the generic claim. In *In re Vaeck*, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991).

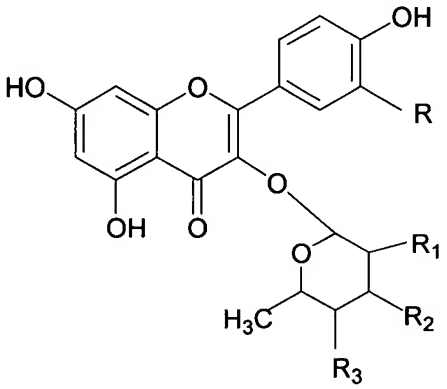
Under the present patent law, claims 21-28 and 32 are enabled under 35 U.S.C. §112, first paragraph. The specification as filed, as well as that known in the art, amply supports these claims because the skilled artisan, armed with the methods disclosed in the specification, the compounds described therein, the methods of making the compounds, the assays as disclosed or known in the art, the cancers as disclosed or known in the art and the assays known for identifying cancers with excessive RSK activity, would have been able to isolate and characterize, through routine experimentation, other compounds having the disclosed biological and biochemical activities as recited by the claims and to test and identify cancers with excessive RSK activity, and to practice the invention commensurate with the scope of the claims without undue experimentation.

Contrary to the assertion of the Examiner that the specification is only enabled for the treatment of prostate cancer and breast cancer, "sarcoma" is also specifically disclosed in the specification and is in fact claimed in previously presented claims 51, 52, and 53. "Sarcoma" was in fact discussed previously by Applicants, where Applicants pointed out on page 17 of the Response filed March 5, 2007 that the Examiner had failed to acknowledge or discuss the term "sarcoma" in the Office Action issued September 5, 2006. The term 'sarcoma' had been added to the claims in the Response dated June 20, 2006 and the Examiner has yet to address the term.

Applicants provide arguments below as to why the specification is enabled for more than three types of cancer, including new data for other cancers from named co-inventors presented in a 37 CFR § 1.132 Declaration submitted herewith, as well as a description of the recently successful treatment of many tumors by others as described in the Declaration. The Declaration further provides data for multiple analogs of SL0101 (a compound of Formula III).

**Regarding independent claim 21**, contrary to the assertion of the Examiner, claim 21 does not recite or encompass all cancers, nor does it recite any Rsk inhibitor. Claim 21 recites:

"A method for treating a **cancer characterized by excessive Rsk activity**, said method comprising the step of **administering to a human or other mammal in need thereof**, a composition comprising **a compound represented by the general structure**:




**III**

wherein R is H or OH, and $R_1$, $R_2$ and $R_3$ are independently selected from the group consisting of hydroxy, $-OCOCH_3$, $-COCH_3$, $C_1$-$C_4$ alkoxy, -O-glucoside and -O-rhamnoside **in an amount effective for specifically inhibiting Rsk activity** in the cells of said human or mammal." (emphasis added).

One of ordinary skill in the art would understand that the phrase "**cancer characterized by excessive Rsk activity**" specifically limits the cancer being treated to only those having excessive Rsk activity, **not** just any cancer, as asserted by the Examiner. One of ordinary skill in the art would understand that the phrase "**administering to a human or other mammal in need thereof**" specifically limits the claim to those humans and other mammals in which such cancers can be treated as claimed, **not** just any cancer, as asserted by the Examiner. Additionally, one of ordinary skill in the art would appreciate that the phrase "**a compound represented by the general structure**" of formula III limits the claims to that structure, **not** to any Rsk specific inhibitor, as asserted by the Examiner. One of ordinary skill in the art would also appreciate that the element "in an amount effective for specifically inhibiting Rsk activity" further limits and defines the claim.

Claims 22, 23, and 24, which depend from claim 21, further define the side groups of the general structure of formula III, although the Examiner did not address claims 22, 23, and 24 specifically.

**Regarding independent claim 25**, contrary to the assertion of the Examiner, claim 25 does not recite or encompass all cancers, nor does it recite any Rsk inhibitor, nor do dependent claims 26, 27, and 28. Claim 25 recites:

"A method for treating **a cancer characterized by excessive Rsk activity**, said method comprising the step of **administering to a patient in need thereof** a composition comprising a **Rsk specific inhibitor** in **an amount effective for specifically inhibiting Rsk activity**." (emphasis added).

One of ordinary skill in the art will appreciate that claim 25 encompasses treating **a cancer characterized by excessive Rsk activity**, **not** just any cancer as asserted by the Examiner. Additionally, one of ordinary skill in the art would understand that the phrase "**administering to a patient in need thereof**" specifically limits the claim to those patients in which such cancers can be treated as claimed, **not** just any cancer, as asserted by the Examiner. Moreover, one of ordinary skill in the art would realize that the inhibitor must be an **Rsk specific inhibitor**, not just any Rsk inhibitor as asserted by the Examiner. It will also be appreciated by one of ordinary skill in the art that the phrase **an amount effective for specifically inhibiting Rsk activity** further defines what is claimed.

Additionally, claim 26, which depends from claim 25, further limits the Rsk specific inhibitor to a compound selected from the group consisting of an anti-sense oligonucleotide and an interfering oligonucleotide. Claim 27, which depends from claim 25, further limits the interfering oligonucleotide to one directed against Rsk1, Rsk2, Rsk3 or Rsk4. Claim 28, which also depends from claim 25, further limits the Rsk specific inhibitor to an extract from the tissues of *Forsteronia refracta* or *Zingiber zerumbet.*

The present specification discloses that a variety of types of molecules can inhibit or reduce Rsk activity, Rsk levels, and in turn inhibit cancer cell proliferation of various kinds of cancer cells but not normal cells, including the use of compounds such as SL0101-1, SL0101-2, SL0101-3 (see figures) and siRNA (see page 36, lines 29-33, and Fig. 7). The invention further provides for other inhibitors, such as compounds comprising the general structures of the compounds of Formulas I and III, short hairpin RNA (page 19, lines 9-18), and antibodies directed against Rsk (see page 22). A 1.132 Declaration provided herewith includes new data

and descriptions of additional references many analogs of SL0101 (i.e., formula III compounds). Regarding Nucleic acid constructs for use in inhibiting Rsk, the application provides adequate enablement. The use of oligonucleotides in general was routine in the art at the time the application was filed, as is indicated by the Examiner's own admission in citing Bjorbaek et al., Marks et al., and Kuijpers et al. (see below in Response to Obviousness rejections). Additionally, recently published articles have used siRNA and other methods to regulate Rsk, cell growth and cancer (see Jackson et al., Cho et al., David et al., Hurbin et al., Anjum et al., Katayama et al., Smith et al., 2005, and Smith et al., 2007, discussed in detail in the 1.132 Declaration submitted herewith).

One of skill in the art would also be able to treat a cancer characterized by excessive Rsk activity by administering an Rsk inhibitor of the invention following the teachings set forth in the specification as filed and/or as known in the art based upon the disclosure provided in the specification without undue experimentation. That is, the crucial teachings of the invention, *inter alia*, discovery of a compound which inhibits Rsk, the role of increased Rsk activity in cancer, and the methods for making such compounds and treating cancer, are amply disclosed in the specification as filed (*see, e.g.*, Examples, and Figures). Therefore, the application merely omits that which is well-known to those skilled in the art and already available to the public, *i.e.*, specific cancers and the methods that a skilled artisan would used to treat such a cancer. Moreover, such compounds are routinely screened in the art and administered and the practice of such methods is routine in the art and should not be considered an undue burden.

Additionally, the present application discloses that Rsk activity is required for proliferation of cancer cells. The present application further provides the first small molecule inhibitor of Rsk activity and shows that the inhibitor functions to halt the growth of the cancer cells, but not normal cells. Thus, the Rsk inhibitor induces the desired physiological response and can therefore be used to treat cancers characterized by over expression of Rsk or over expression of Rsk activity compared to that observed in the non-diseased tissue.

The teachings embodied in this application were not part of the state of the art at the time of filing. In fact, the present application demonstrates that the compounds described herein: 1) selectively inhibit cancer cell proliferation relative to normal cells and that the inhibition is reversible (see Figures 4, 7, 8); 2) that the compounds inhibited Rsk catalytic activity (See

Figures 2, 3, 5); and 3) that the compounds inhibited Rsk2 kinase activity (see Figures 6, 10). The present application further discloses enzyme specificity of the compounds. Significantly, SL0101-1, -2, and -3 do not inhibit the evolutionarily related p70 S6 kinase and Mitogen and Stress-activated Protein Kinase (MSK). In addition, they do not inhibit the prototypical serine/threonine kinase Protein Kinase A or the tyrosine kinase Focal Adhesion Kinase (FAK) (Figure 3).

Additionally, assays such as high throughput assays are provided for screening and testing such compounds, the specification provides methods for purifying and/or synthesizing and testing compounds. For example, **1500 extracts** were easily assayed when screening and discovering the *Forsteronia refracta* activity which inhibits Rsk activity (see page 10, lines 6-8, page 31, lines 3-28, and page 32, lines 5-8). Such assays are routine in the art and do not require undue experimentation. Additionally, "effective amount" is discussed at page 5, lines 5-9, to mean an amount sufficient to produce a selected effect. For example, an effective amount of an Rsk inhibitor is "an amount of the inhibitor sufficient to suppress Rsk activity. Suppression of Rsk activity can be detected, for example, through the use of a serine/threonine kinase assay, such as the kinase assay described in Example 3". The specification as filed also describes methods for purifying such compounds, as well as synthesizing such compounds.

**New Data as Provided in the 37 CFR § 1.132 Declaration of named inventors Smith and Lannigan**

Figures 1-3 of the 1.132 Declaration provide further Rsk expression data with additional cancers, further demonstrating that Rsk1 and/or Rsk2 are expressed at higher levels in the cancer. These data further indicate that through routine experimentation a cancer can be easily identified which has excessive RSK activity.

Importantly, Table 1 of the Declaration shows the potency of SL0101 and **seven analogs** of SL0101 in kinase assays. These new data further demonstrate that through routine experimentation analogs of SL0101 can be made and tested which can inhibit cancer cell growth of cancers exhibiting excessive Rsk activity.

Even more importantly, Table 2 provides data for successfully treating **multiple** cancers with analog 5 of SL0101 (see Table 1 of Declaration). **Thirty** cancers, including those from nine different tissue types were tested successfully, including four leukemias, six lung cancers, four

colon cancers, two central nervous system cancers, three melanomas, two ovarian cancers, five renal cancers, one prostate cancer, and three breast cancers. The data in the Declaration provide further evidence that only routine experimentation is needed to prepare and test inhibitors of Rsk activity, and that only routine experimentation is needed to test cancers for excessive Rsk activity before treating them. One of ordinary skill in the art will appreciate that identification of those signaling events that are aberrantly regulated in a tumor is essential for the proper diagnosis of the tumor and treatment. Therefore, identifying whether the tumor is characterized by excessive Rsk activity represents the MINIMAL experimentation required for proper treatment of the cancer, as is claimed.

Additionally, the 1.132 Declaration provides a series of references and explanations regarding recently published articles which corroborate the findings and support the claims herein. These references are:

Hayashi et al., Cancer Res., 2005, 657699; Jackson et al., J. Biol. Chem., 2005; Cho et al., Cancer Res., 2007, 67:8104; Cuadrado et al., Cancer Cell, 2007, 12:187; David et al., J. Clin. Invest., 2005, 115:664; Hurbin et al., J. Biol. Chem. 2005, 280:19757; Anjum et al., Curr. biol., 2005, 15:1762; Katayama et al., mol. cancer Ther., 2007, 6:3108; Smith et al., Cancer Res., 2005, 65:1027; Smith et al., Bioorg. Med. Chem. 15:5018.

The references are described in detail in the 1.132 Declaration submitted herewith and are supplied with an IDS herewith.

Experimentation is not undue if it is the type of experimentation that is routinely performed in the art. The authors have demonstrated that multiple SL0101 analogs are effective at inhibiting proliferation of various cancer cells. These data buttress the claim that numerous SL0101 analogs are useful as Rsk inhibitors and anti-tumor agents. Applicants assert that the minimal experimentation required herein would not be undue, particularly based on the limitations recited in the claims and the fact that the specification as filed, the Declaration provided herewith, and the additional papers cited in the Declaration all show that the treatment of cancer is enabled by the specification as filed.

**Response to Rejection of Claims 21-24, 32, and 51-53 under 35 U.S.C. § 103(a), obviousness**

Claims 21-24, 32 and 51-53 stand rejected as allegedly obvious over Matthes et al. (Phytochemistry, 1980, 19, 2643-2650), in view of Bjorbaek (WO 00/66721), Marks (U.S. 5,910,583), Kuijpers (U.S. 5,733,523) and Pienta et al. (Anticancer Research, 1994, 14, 2617-2619).

Applicants note that "Pienta et al." is really "Naik et al.". Pienta is the senior author.

Applicants also note that claim 53 does not depend from independent claim 21, as do the rest of the claims recited in this section. However, Applicants will address the rejection of claim 53 here anyway.

It is the view of the Examiner that Matthes discloses a compound of structural formula 7, wherein two of the three hydroxyl groups on the sugar moiety are acetylated (citing page 2645). The Examiner then asserts that this compound is structurally the same as the compound claims in instant claims 21-24 and 52. The Examiner further asserts that Matthes teaches that the extract from the roots of Zingiber zerumbet was tested against a rat neoplastic liver cell strain and found to be cytotoxic (citing page 2643, left column, and Introduction, second and third paragraphs). The Examiner then admits that even though Matthes teaches a compound that shows cytotoxicity toward neoplastic cells and a composition, Matthes does not teach a that the compound of Matthes is an Rsk inhibitor.

It is the view of the Examiner that Bjorbaek teaches inhibition of Rsk activity using nucleic acid construct expressing Rsk2 or a biologically active fragment thereof (citing page 2, line 26 through page 4, line 3; page 21 lines 1-7; example at pages 24-31). However, the Examiner admits that Bjorbaek does not teach a composition comprising the nucleic acid constructs as anticancer agents.

It is the opinion of the Examiner that Kuijpers teaches in general the use of antisense oligonucleotides and their pharmaceutical formulations for the treatment of tumors. It is also the opinion of the Examiner that Marks teaches a variety of used for oligonucleotides for treating tumors.

The Examiner then asserts that based on the prior art teachings cited, one of ordinary skill in the art will recognize that:

1. Nucleic acid constructs can be used to inhibit Rsk activity and antisense-oligonucleotides have been used for cancer treatment. Therefore, antisense-oligonucleotides and interfering oligonucleotides can be used for treating cancer by inhibiting Rsk activity.

2. Flavonoid glycoside of Matthes exhibits anti-neoplastic activity and like oligonucleotides can be used for inhibiting Rsk activity and hence inhibition of cell proliferation of cancer.

The Examiner then asserts at page 9 that one of skill in the art would be motivated to use the compounds of they type taught by Matthes, since Pienta (Naik) teaches that flavone compounds have anticancer properties (citing page 2617, left column, first two paragraphs).

The Examiner goes on to discuss similarity of structure and function of compounds and motivation and expectations of using them. Examiner asserts that where a prior art compound essentially brackets the claimed compounds and are well know anticancer/antitumor agents, one of ordinary skill in the art would be motivated to make the claimed compounds in searching for new anticancer/antitumor agents (citing In re Payne, 606, F.2d 303, 203, USPQ, 245, 254-55 (C.C.P.A. 1979).

Applicants traverse the rejection and respectfully submit that Matthes et al. (Phytochemistry, 1980, 19:2643) in combination with Bjorbaek et al. (WO 00/66721), Marks et al. (U.S. Pat. No. 5,910,583), Kuijpers et al. (U.S. Pat. No. 5,733,523), and Naik et al. (Pienta) (Anticancer Res., 1994, 14:2617-2620) does not render any of the present claims *prima facie* obvious under 35 U.S.C. § 103(a) for the following reasons:

Preliminarily, the three-prong test which must be met for a reference or a combination of references to establish a *prima facie* case of obviousness has not been satisfied in the instant matter. The MPEP states, in relevant part:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. MPEP § 2142.

Additionally, MPEP § 2143.01 provides: "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)" (emphasis added). However, the TSM test must not be rigidly applied (KSR Intern. Co. v. Teleflex Inc., 127 S.Ct. 1727 (2007)), but to determine whether there is an apparent reason to combine the known elements in the fashion as claimed, the analysis should be made explicit by the Examiner (*Id*).

None of these criteria have been met here.

It appears that the Examiner is under the impression that it was known in the prior art that Rsk activity, particularly excessive Rsk activity, is connected to cancer. That is not the case, and in fact was an unexpected result disclosed in the present application. Otherwise, the Examiner is using impermissible hindsight to render an obviousness rejection. The data disclosed in the present application were the first to correlate Rsk activity with cancer and therefore, regardless of the techniques known in the prior art, it would not be obvious to inhibit Rsk activity by any manner to treat cancers until this invention was published. Rather than being obvious, it is highly improbable that one skilled in the art would combine any prior art and use an Rsk inhibitor as an anti-tumor agent because the present invention was the first to identify a correlation between Rsk activity and cancer. These assertions of the Applicants are more fully detailed below.

First, at the time the application was filed there was no knowledge in the art that cancer cells had excessive Rsk activity. The Applicants disclosed that cancer cells can have excessive Rsk activity. Second, the Applicants were to first to show a relation between Rsk activity and cell proliferation. Third, the Applicants were the first to show that the various compounds and molecules disclosed herein, even those known to impact Rsk, had antitumor activity.

Applicants assert that there would be no motivation to modify or combine the references cited by the Examiner, and that even if combined, the result is not each and every element of the claims.

Contrary to the assertion of the Examiner, Matthes teaches that compounds 4, 5, and 6 are "highly cytotoxic", but that compound 7 was "slightly cytotoxic". Applicants assert that these results teach away from the use of compound 7, and that one of ordinary skill in the art would be

motivated to use compounds such as 4, 5, or 6, instead of 7. In fact, Matthes demonstrated that at least nine different compounds were 3 to 4 fold more cytotoxic than compound 7 (see Table 1 of Matthes). For these reasons, there would be no motivation to use compound 7 of Matthes as claimed in the present application. Additionally, there is no motivation or suggestion provided in Matthes to modify Matthes or to combine the teachings of Matthes with the other references cited by the Examiner, particularly since the teachings of Matthes would instead suggest the use of compounds 4, 5, or 6, which are not similar to the compounds claimed. Thus, because Matthes provides neither evidence that compound 7 is an Rsk-specific inhibitor nor that Rsk-specific inhibition stops the growth of tumor cells, it would not be obvious to apply Matthes' teachings of a compound "with no anti-HIV or anti-tumor activity" for use as a pharmacological inhibitor of Rsk and an anti-tumor agent. Additionally, as admitted by the Examiner, Matthes does not teach that compound 7 is an Rsk inhibitor.

Furthermore, Matthes does not disclose, suggest, teach, or even contemplate, compositions or methods useful for treating cancer, wherein the cancer has excessive Rsk activity, wherein the composition is an Rsk specific inhibitor (as in claim 53), wherein it is a compound as in claim 21, wherein a compound as in claim 21 is further combined with an additional antitumor agent (claim 32), or where the compound is further refined as in claims 22-24 and 52, or where specific cancers such as breast cancer, prostate cancer, and sarcoma are treated as in claim 51.

Applicants also assert that additional studies were later published by the National Cancer Institute, which indicated that compound 7 of Matthes, which is also called 3",4"-O-Deacetylafzelin by Matthes, has no anti-HIV activity and no antitumor activity (Dai et al., 1997, Natural Product Letters, 10:115-118; a copy of which is provided herewith with a Supplementary IDS). In fact, Dai discloses that none of the afzelins were active in either assay (see abstract). These data are also published at the National Cancer Institute website for Molecular Targets Development Program, which provides the afzelin structure and indicates that it is a natural product **without** anti-HIV and antitumor activity. That listing also cites Dai. The URL for the NCI website page is http://home.ncicrf.gov/mtdp/Catalog/compounds/703082.html. The compound is also labeled as NSC 703082. A copy of the website page is also provided herewith.

The disclosure of Dai, as well as the listing at the National Cancer Institute database, teaches away from the use of the compounds of claim 21 of the present invention, as does the data of Matthes which shows little activity for their compound 7, relative to their other compounds such as 4, 5, and 6. Therefore, the art at the time this application was filed taught away from the use of such compounds as claimed. Because Matthes and similar art taught away from the present invention, there would be no motivation or suggestion to combine Matthes with other references, nor would there be a reasonable expectation of success.

Regarding Bjorbaek, it does not correct the deficiencies of Matthes and in fact is not even applicable to claims 21-24, 32 and 51-52 because those claims only recite using compounds such as those derived from formula III and do not recite any nucleic acids. Bjorbaek merely measured physical and weight characteristics of mice which had a deletion of the Rsk2 gene. Bjorbaek provided no data regarding regulation of Rsk. Bjorbaek merely speculated regarding Rsk regulation and weight control. These teachings would provide no reason, motivation, or suggestion that Rsk is associated with cancer or that excessive Rsk activity is associated with cancer, or even that Rsk activity is associated with cell proliferation. Furthermore, the teachings of Bjorbaek regarding nucleic acid constructs would not motivate one of ordinary skill in the art to use compounds of formula III and the SL0101 analogs such as those claimed in claimed 21 and it dependent claims.

Furthermore, Bjorbaek does not disclose, suggest, teach, or even contemplate, compositions or methods useful for treating cancer, wherein the cancer has excessive Rsk activity, wherein the composition is an Rsk specific inhibitor (as in claim 53), wherein it is a compound as in claim 21, wherein a compound as in claim 21 is further combined with an additional antitumor agent (claim 32), or where the compound is further refined as in claims 22-24 and 52, or where specific cancers such as breast cancer, prostate cancer, and sarcoma are treated as in claim 51.

Bjorbaek made no distinction between excessive Rsk activity and normal Rsk activity. Furthermore, Bjorbaek only addressed Rsk2, and not other Rsks, as taught and claimed herein. Rsk4 was not even known at the time of Bjorbaek, and the antisense sequence directed against Rsk4 disclosed in the present application is novel. At page 2, as cited by the Examiner, Bjorbaek merely speculates about "regulating" Rsk. Bjorbaek does not even speculate about inhibiting

Rsk. Furthermore, at page 21, lines 1-7, cited by the Examiner, Bjorbaek specifically speculates about methods to "increase" the activity of Rsk (see page 21, line 1). The method claims of the present application all encompass "inhibiting" or decreasing Rsk activity, not increasing the activity as suggested by Bjorbaek. Therefore, Bjorbaek at page 21 lines 1-7 teaches away from the present invention.

Bjorbaek merely speculated about inhibiting Rsk, but did not disclose inappropriate Rsk activity or actually make or use any Rsk inhibitors. Therefore, there would be no motivation to combine any of the compounds of the invention, which are claimed to be Rsk specific inhibitors, with any other agent, regardless of what type of agent it is, particularly because Bjorbaek teaches away from the present invention.

Applicants assert that Kuijpers does not correct the deficiencies of Matthes, nor does it correct the deficiencies of Bjorbaek. Kuijpers encompasses radioactively labeled oligonucleotides useful for directly targeting these radioactive molecules to a location for uses such as radiation therapy. Kuijpers does not teach specific sequences useful for inhibiting activity, much less teach antisense oligonucleotides directed against Rsks. Kuijpers does not even address Rsk activity, nor disease or conditions which can be treated with inhibitors of Rsk activity.

Kuijpers does not disclose, suggest, teach, or even contemplate, compositions or methods useful for treating cancer, wherein the cancer has excessive Rsk activity, wherein the composition is an Rsk specific inhibitor (as in claim 53), wherein it is a compound as in claim 21, wherein a compound as in claim 21 is further combined with an additional antitumor agent (claim 32), or where the compound is further refined as in claims 22-24 and 52, or where specific cancers such as breast cancer, prostate cancer, and sarcoma are treated as in claim 51.

Kuijpers provides no reason, motivation or suggestion to modify the teachings therein or to combine the teachings therein with other art, including the art cited by the Examiner to arrive at the present invention. Furthermore, even if Matthes and Bjorbaek were combined, and Kuijpers were also combined with these references, the result would not be the present invention as claimed.

Marks does not correct the deficiencies of Matthes, Bjorbaek, or Kuijpers. Marks is directed to antisense oligonucleotides directed against the ERBB2 oncogene. Marks does not

disclose, suggest, teach, or even contemplate, compositions or methods useful for treating cancer, wherein the cancer has excessive Rsk activity, wherein the composition comprises an Rsk specific inhibitor (as in claim 53), wherein it is a compound as in claim 21, wherein a compound as in claim 21 is further combined with an additional antitumor agent (claim 32), or where the compound is further refined as in claims 22-24 and 52, or where specific cancers such as breast cancer, prostate cancer, and sarcoma are treated as in claim 51.

Marks provides no reason, motivation or suggestion to combine the teachings therein with the teachings of Matthes, Bjorbaek, or Kuijpers. Furthermore, it would not be obvious to combine the teachings of Matthes, Bjorbaek, Kuijpers, or Marks for the reasons discussed above. Additionally, it would not be obvious to modify Matthes in view of Bjorbaek, Kuijpers, and Marks for the reasons discussed above. First, none of the references discloses that excessive Rsk activity is involved in cancer or any other type of cell proliferation. Therefore, there would be no motivation to use inhibitors of Rsk to treat inappropriate Rsk activity, because inappropriate Rsk activity was not contemplated to be associated with cancer in any of the four references. Additionally, none of the compounds presently claimed were known to be Rsk inhibitors. Furthermore, as described above, it is evident that even if the cited references were combined, the result is not the invention as claimed, because the references do not teach or disclose each and every element of the claims.

Pienta (Naik) does not correct the deficiencies of the other references and in fact, contrary to the assertion of the Examiner, Pienta (Naik) teaches away from the present application. Although Pienta (Naik) did find genistein to be somewhat effective in vitro on cancer cells, when they tested it in vivo they got absolutely no effect at all on tumor growth in animals (see abstract and examples). For example, in the abstract Pienta states "In vivo, however, genistein failed to significantly inhibit the growth of subcutaneously implanted MAT-LyLu cells" (a transplantable prostate tumor). Thus, one of ordinary skill in the art would not be motivated to use genistein or any similar compound to treat cancer in vivo when it failed to work in vivo as taught by Pienta (Naik). In fact, one of ordinary skill in the art would be motivated to **not** use such a drug.

Additionally, Pienta (Naik) does not disclose, suggest, teach, or even contemplate, compositions or methods useful for treating cancer, wherein the cancer has excessive Rsk

activity, wherein the composition is an Rsk specific inhibitor (as in claim 53), wherein it is a compound as in claim 21, wherein a compound as in claim 21 is further combined with an additional antitumor agent (claim 32), or where the compound is further refined as in claims 22-24 and 52, or where specific cancers such as breast cancer, prostate cancer, and sarcoma are treated as in claim 51.

Pienta provides no reason, motivation, or suggestion to combine the teachings therein with the teachings of Matthes, Bjorbaek, Kuijpers, or Marks. Furthermore, it would not be obvious to combine the teachings of Matthes, Bjorbaek, Kuijpers, Marks and Pienta for the reasons discussed above. Additionally, it would not be obvious to modify Matthes in view of Bjorbaek, Kuijpers, Marks and Pienta for the reasons discussed above. First, none of the references discloses that excessive Rsk activity is involved in cancer or any other type of cell proliferation. Thus, there would be no motivation to use inhibitors of Rsk to treat inappropriate Rsk activity, because inappropriate Rsk activity was not contemplated to be associated with cancer in any of the five references. Additionally, none of the compounds presently claimed were known to be Rsk inhibitors.

In order for a reference or combination of references to render a claim obvious, the reference(s) must teach each and every element of the claim and the references cited by the Examiner do not. For example, independent claim 21 recites:

"A method for treating a **cancer characterized by excessive Rsk activity**, said method comprising the step of **administering to a human or other mammal in need thereof**, a composition comprising **a compound represented by the general structure** (of formula III), wherein R is H or OH, and $R_1$, $R_2$ and $R_3$ are independently selected from the group consisting of hydroxy, -$OCOCH_3$, -$COCH_3$, $C_1$-$C_4$ alkoxy, -O-glucoside and -O-rhamnoside **in an amount effective for specifically inhibiting Rsk activity** in the cells of said human or mammal."

None of the references teach or contemplate or suggest, alone or in combination, a method of treating a **cancer characterized by excessive Rsk activity**, ***and using*** **a compound represented by the general structure** (of formula III), ***and*** administering the composition such that the compound is **in an amount effective for specifically inhibiting Rsk activity**, as recited in claim 21. Nor do the references suggest the structural limitations of formula III recited in dependent claims 22, 23, 24, 32, and 51-53.

For the reasons discussed above, Applicants submit that claims 21-24, 32, and 51-53 are not obvious and request that the rejection as to these claims be withdrawn.

**Response to Rejection of Claims 25-27 under 35 U.S.C. § 103(a), obviousness**

Claims 25-27 stand rejected as allegedly obvious over Bjorbaek (WO 00/66721) in view of Marks (U.S. 5,910,583) and Kuijpers (U.S. 5,733,523).

It is the view of the Examiner that Bjorbaek teaches, inter alia, inhibition of Rsk activity using nucleic acid construct expressing Rsk2 or a biologically active fragment thereof (citing page 2, line 26 through page 4, line 3; page 21 lines 1-7; example at pages 24-31). However, the Examiner admits that Bjorbaek does not teach a composition comprising the nucleic acid constructs as anticancer agents.

It is the opinion of the Examiner that Kuijpers teaches in general the use of antisense oligonucleotides and their pharmaceutical formulations for the treatment of tumors. It is also the opinion of the Examiner that Marks teaches a variety of used for oligonucleotides for treating tumors.

The Examiner then asserts that based on the prior art teachings cited, one of ordinary skill in the art at the time the invention was made, it would have been obvious to use antisense oligonucleotides and interfering oligonucleotides as Rsk specific inhibitors for the treatment of cancer since oligonucleotides have been used for the treatment of cancer and nucleic acid constructs are also known to inhibit Rsk activity.

The Examiner further asserts that one of ordinary skill in the art would be motivated to use the composition comprising an Rsk specific inhibitor in the method as instantly claimed since Rsk inhibition in to addition to treating cancer also has other beneficial effects as taught by Bjorbaek.

Applicants traverse the rejection and respectfully submit that Bjorbaek et al. (WO 00/66721), Marks et al. (U.S. Pat. No. 5,910,583), and Kuijpers et al. (U.S. Pat. No. 5,733,523), do not render any of the present claims *prima facie* obvious under 35 U.S.C. § 103(a) for the following reasons:

As discussed above, it appears that the Examiner is under the impression that it was known in the prior art that Rsk activity, particularly excessive Rsk activity, is connected to

cancer. At the time the application was filed, there was no knowledge in the art that cancer cells had excessive Rsk activity. The Applicants in fact disclosed in the present application that cancer cells can have excessive Rsk activity. Second, the Applicants were to first to show, in the present application, that there is a relation between Rsk activity and cell proliferation. Third, the Applicants were the first to show that the various classes compounds and molecules disclosed herein had antitumor activity.

Applicants assert that there would be no reason or motivation to modify or combine the references cited by the Examiner, and that even if combined, the result is not each and every element of the claims. Claim 25 recites:

"A method for treating **a cancer characterized by excessive Rsk activity**, said method comprising the step of **administering to a patient in need thereof** a composition comprising a **Rsk specific inhibitor** in **an amount effective for specifically inhibiting Rsk activity**." (emphasis added)

Claims 26 and 27, which depend from claim 25, recite that the Rsk inhibitor is an anti-sense oligonucleotide or an interfering nucleotide (26) or is an interfering RNA directed against Rsk1, 2, 3, or 4 (27). For the references to render the claims obvious, they must teach or suggest all of the claim limitations, and these references do not.

The arguments applied above for Bjorbaek apply with equal force here. Bjorbaek does **not** disclose, suggest, teach, or even contemplate, compositions or methods useful for treating cancers characterized by excessive Rsk activity, wherein the composition is an Rsk specific inhibitor, wherein it is an agent as in claim 25, where the inhibitor is an anti-sense oligonucleotide or an interfering oligonucleotide (claim 26), or is an interfering RNA directed against Rsk1, 2, 3, or 4 (claim 27). Bjorbaek does **not** address cancer or address excessive Rsk activity, nor discuss anything other than possibly regulating Rsk activity. Bjorbaek made no distinction between excessive Rsk activity and normal Rsk activity. Furthermore, Bjorbaek only addressed Rsk2, and not other Rsks, as taught and claimed herein (for example, see claim 27). Rsk4 was not even known at the time of Bjorbaek, and the antisense sequence directed against Rsk4 disclosed in the present application is novel. At page 2, as cited by the Examiner, Bjorbaek merely speculates about "regulating" Rsk. Bjorbaek does not even speculate about inhibiting Rsk. Furthermore, at page 21, lines 1-7, cited by the Examiner, Bjorbaek specifically speculates

about methods to "increase" the activity of Rsk (see page 21, line 1). The method claims of the present application all encompass "inhibiting" or decreasing Rsk activity, not increasing the activity as suggested by Bjorbaek. Therefore, Bjorbaek at page 21 lines 1-7 teaches away from the present invention.

Applicants also assert that Marks does not correct the deficiencies of Bjorbaek. Marks is directed to antisense oligonucleotides directed against the ERBB2 oncogene. Marks does not disclose, suggest, teach, or even contemplate, compositions or methods useful for treating cancers wherein the composition is an Rsk specific inhibitor, wherein it is a compound or agent as in claim 25, where the inhibitor is an anti-sense oligonucleotide or an interfering oligonucleotide (claim 26), or is an interfering RNA directed against Rsk1, 2, 3, or 4, or the inhibitor is a plant extract (claims 27 and 28).

Marks provides no reason, motivation or suggestion to combine the teachings therein with the teachings of Bjorbaek. Furthermore, it would not be obvious to combine the teachings of Bjorbaek or Marks for the reasons discussed above. Additionally, it would not be obvious to modify Bjorbaek in view of Marks for the reasons discussed above. First, none of the references discloses that excessive Rsk activity is involved in cancer or any other type of cell proliferation. Therefore, there would be no motivation to use inhibitors of Rsk to treat excessive Rsk activity in cancer cells, because inappropriate Rsk activity was not contemplated to be associated with cancer in any of the three references. Additionally, none of the compounds presently claimed were known to be Rsk inhibitors.

Applicants assert that Kuijpers does not correct the deficiencies of Bjorbaek or Marks. Kuijpers encompasses radioactively labeled oligonucleotides useful for directly targeting these radioactive molecules to a location for uses such as radiation therapy. Kuijpers does not teach specific sequences useful for inhibiting activity, much less teach antisense oligonucleotides directed against Rsks. Kuijpers does not address Rsk activity, nor disease or conditions which can be treated with inhibitors of Rsk activity.

Kuijpers does not disclose, suggest, teach, or even contemplate, compositions or methods useful for treating diseases or condition wherein the composition is an Rsk specific inhibitor as in claim 25, or where the inhibitor is an anti-sense oligonucleotide or an interfering

oligonucleotide (claim 26), or is an interfering RNA directed against Rsk1, 2, 3, or 4, or the inhibitor is a plant extract (claims 27 and 28).

Kuijpers provides no motivation or suggestion to modify the teachings therein or to combine the teachings therein with other art, including the art cited by the Examiner to arrive at the present invention. Furthermore, even if Bjorbaek, Marks and Kuijpers were combined, the result would not be the present invention as claimed.

As described above, it is evident that even if the cited references were combined, the result is not the invention as claimed, because the references do not teach or disclose each and every element of the claims.

For the reasons discusses above, Applicants submit that the cited references do not render obvious any claim in the application and request that the rejection as to claims 25-27 be withdrawn.

**Claims free of the Prior Art**

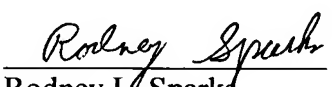
Applicants note that claim 28 was not rejected in either 103 rejection, thus it is free of the prior art.

Conclusion

Applicants respectfully submit that all claims are fully enabled, free of the art, not obvious, and are in condition for allowance. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (434) 243-6103.

Respectfully submitted,

Date: September 19, 2007



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